IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Sabine FRICKE

Group Art Unit: 1617

Serial No.: 10/798,780 :

Examiner: San Ming HUI

Filed: March 12, 2004 :

For: METHODS AND PHARMACEUTICAL COMPOSITIONS FOR RELIABLE ACHIEVEMENT OF ACCEPTABLE SERUM TESTERONE LEVELS

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Sabine Fricke, being duly warned, declare that:

I am a citizen of Germany, residing in Jena, Germany.

I am an inventor of the above-captioned application and am, therefore, familiar with the invention described therein and with the grounds for rejection made against the claims of the application in the Office Action mailed November 15, 2007, from the U.S. Patent and Trademark Office. My expertise for making this declaration is further demonstrated in the attached CV.

If a patent issues from this application and if it is decided by the assignee to pursue a commercial product falling under its claims and if such a commercial product is approved by FDA and sold in the US, then under German law, I and the other inventors will receive some income derived from such sales.

The experiments described herein were conducted by me or under my supervision.

Experiments were conducted to assess the solubility of testosterone undecanoate (TU) in

different oils. Different benzyl benzoate/oil mixtures that contained 250 mg TU per ml were studied as to their crystallizability in a refrigerator (at 2-8°C). It was to be determined which particular oil and which ratio of concentrations of benzyl benzoate/oil had the highest TU-dissolving capacity.

Materials

Refined castor oil for parenteral use: DAB [*German Pharmacopoeia*]

Peanut oil for parenteral use: Ph. Eur.

Miglyol 812: Ph. Eur.

Benzyl benzoate: Ph. Eur., USP

Testosterone undecanoate: Internal Monograph

Preparation

To prepare each of the test solutions, 25 g TU were dissolved at 50°C in the respective amount of benzyl benzoate, whereupon the amount of the respective oil was added. The resultant mixture was then stirred. A clear solution had to be formed. Ampoules were each filled with 4 ml of part of the solution and then closed. Eight of the closed ampoules were kept in a refrigerator (at 2-8°C) and 4 ampoules were kept at 25°C. The ampoules were checked at specific times for the presence of any precipitate (crystals).

Mixing ratios:

25 g TU in a mixture of 40% benzyl benzoate + 60% refined castor oil

25 g TU in a mixture of 50% benzyl benzoate + 50% refined castor oil

25 g TU in a mixture of 63% benzyl benzoate + 37% refined castor oil

25 g TU in a mixture of 40% benzyl benzoate + 60% peanut oil

25 g TU in a mixture of 50% benzyl benzoate + 50% peanut oil

25 g TU in a mixture of 63% benzyl benzoate + 37% peanut oil

25 g TU in a mixture of 40% benzyl benzoate + 60% Miglyol 812

25 g TU in a mixture of 50% benzyl benzoate + 50% Miglyol 812

25 g TU in a mixture of 63% benzyl benzoate + 37% Miglyol 812

Results:

Stability of the oily solutions at room temperature (25°C)

The solutions were considered stable if there was exhibited no precipitate (crystals) in the ampoule after 34 days time. The data are shown in the attached table. The only solution which maintained sufficient solubility in the tests was a solution containing TU in a 37% castor oil and 63% cosolvent oily solution.

The data demonstrate that castor oil is surprisingly advantageous to other oils for providing a stable solution of TU. Further, the data demonstrate that castor oil is surprisingly advantageous when used in a lower concentration relative to the cosolvent, as opposed to higher concentrations previously thought to be necessary.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and

that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

15.01.2008
Date

Sabine Fricke
Dr. Sabine Fricke

Stability of the oily solutions during storage in a refrigerator (at 2-8 °C)

Formulations containing refined castor oil for parenteral use	Number of ampoules with precipitation (crystals) after								
	0 d	1 d	2 d	3 d	6 d	8 d	10 d	21 d	34 d
40% benzyl benzoate	0	5	6	6	6	6	6	6	6
50% benzyl benzoate	0	0	1	3	3	3	3	4	5
63% benzyl benzoate	0	0	0	0	0	0	0	0	0

Formulations containing peanut oil for parenteral use	Number of ampoules with precipitation (crystals) after						
	0 d	1 d	4 d	6 d	8 d	19 d	32 d
40% benzyl benzoate	0	5	6	6	7	8	8
50% benzyl benzoate	0	2	5	5	5	7	8
63% benzyl benzoate	0	0	5	5	5	7	8

Formulations containing Miglyol 812 for parenteral use	Number of ampoules with precipitation (crystals) after							
	0 d	1 d	2 d	5 d	7 d	9 d	20 d	33 d
40% benzyl benzoate	0	4	4	7	8	8	8	8
50% benzyl benzoate	0	1	1	8	8	8	8	8
63% benzyl benzoate	0	0	1	1	1	1	5	6

It can be said in conclusion that the formulation that contains refined castor oil for parenteral use with a percentage of 63% benzyl benzoate (= composition of the original Nebido®-formulation) is the only formulation in which TU does not precipitate during storage over 34 days in a refrigerator (at 2-8°C). All other tested oils and, respectively, mixing ratios give an unstable product.

Curriculum vitae

Dr. Sabine Fricke
Birthdate: February 18,1949
Address: An der Riese 1 b, 07749 Jena, Germany

Current position:
Head of Pharmaceutical and Analytical Development, Jenapharm, Jena, Germany

Education:

1963	University entrance-diploma and certificates as lab assistant
1967-1972	Study of pharmacy at the universities in Jena and Halle/Saale
1972	State examination and diploma
1973	Approval as pharmacist (Approbation als Apotheker)
1979	Specialist for pharmaceutical technology (Fachapotheker)
1988	Ph.D. (Dr.rernat.) in pharmaceutical technology, university Halle/Saale, Germany
1994	Approval as head of production and head of quality control
1994	Approval as education specialist for pharmaceutical technology (Ausbildungsbeauftragte)

Job history

1972-1988	Scientific assistant at department "Galenik"Jenapharm	2 direct reports
1988-2000	Head of Jenapharm´s sterile and special formulations group in the department "Galenik"	5 direct reports 8 total
2000-2005	Head of Jenapharm´s department "Pharmaceutics" (parenteral and oral solid dosage forms)	3 direct reports 20 total
January 1, 2006	Head of pharmaceutical and analytical development Jenapharm	5 direct reports total 35

Scientific focus:

- Galenical development of parenteral, oral and special formulations
- Steroidal formulations, esp. injectable formulations and oral solid dosage forms with an immediate and modified release
- Freeze dried products
- Clinical supplies (phase I-III)

Publications/patents
Papers/ lectures: appr. 100
Patents: 15
Coauthor of the Schriftenreihe des BAH:

- „Qualifizierung und Prozessvalidierung", 3. Auflage 2006
- „Leitfadens zur Durchführung von Audits" 1. Auflage 2006

Membership of scientific societies:
APV
Deutsche Pharmazeutische Gesellschaft

Teaching activities:

1993-1994	Special lecture in pharmaceutical technology I on the Friedrich-Schiller-University Jena
1995	Teaching position for pharmaceutical technology I on the Friedrich-Schiller-University Jena
1996	Teaching position for pharmaceutical technology for Prof. Westesen on the Friedrich-Schiller-University Jena

Jena, January, 2008 Sabine Fricke